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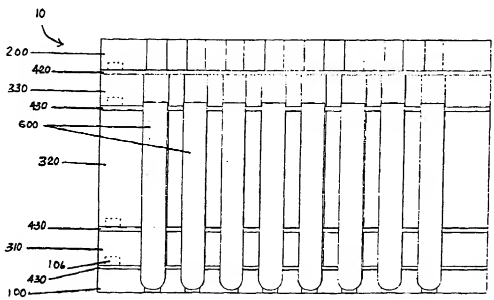

(57) Abstract

A modular apparatus (10) for chemical synthesis in which a wide variety of different orgnic chemical reactions can be carried out simultaneously in a collection of simple reaction vessels (500) is disclosed. A modular apparatus (10) comprising a reaction block (100) with an upper surface (102) having an array of uniformly sized depressions (101) in the surface, each depression having a fixed shape and area at the surface; and at least one function block (310, 320, 330, 360, 370, 600) having an upper surface and a lower surface, wherein the function block (310, 320, 330, 360, 370, 600) has a plurality of through passages (301) from the function block upper surface to the function block lower surface arranged in an array to match the array in the reaction block (100), whereby the reaction block (100) and the function block or blocks (310, 320, 330, 360, 370, 600) together form a collection of interior spaces in the apparatus for holding a plurality of reactions vessels therein is disclosed.

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SIMULTANEOUS CHEMICAL REACTION APPARATUS

INTRODUCTION

Technical Field

The invention relates to an apparatus and related methods used for the simultaneous synthesis of chemical compounds in separate reaction chambers, either in solution or involving solid-phase chemical reactions on a substrate, especially, although not limited to, synthesis of organic chemical compounds whose synthesis involves a reaction step under reflux.

Background

Peptides and oligonucleotides have long been synthesized in parallel using various apparatus configurations, and a brief review of the background of simultaneous peptide and oligonucleotide synthesis is helpful in understanding the background of the present invention, although it will be apparent from this review that the problems associated with "biochemical" syntheses are different from the problems associated with traditional organic syntheses, particularly those involving reflux in a boiling organic solvent.

In a basic, single synthesis of a peptide as most commonly practiced, amino acids are sequentially coupled to a functionalized solid support. Several methods have been developed by which peptides or oligonucleotides may be simultaneously synthesized in parallel. One such methodology for peptide synthesis was disclosed in Geysen et al, International Publication Number WO 90/09395. Geysen's method involves functionalizing the termini of polymeric rods and sequentially immersing the termini in solutions of individual amino acids. Geysen's approach has proven to be impractical for commercial production of peptides because only very minute quantities of polypeptides can be generated. In addition, this method is too labor intensive for extensive or commercial use. A second method of peptide or oligonucleotide synthesis was developed by Affymax Technologies N.V. and disclosed in U.S. Pat. No. 5,143,854. The Affymax method involves sequentially using light for illuminating a plurality of polymer sequences on a substrate and delivering reaction fluids to the substrate. This method of synthesis has numerous drawbacks, including the fact that the products are noncleavable and that the process produces large numbers, but only minute quantities, of products. A further method and device for producing peptides or oligonucleotides is disclosed in Houghton, European Patent Number 196174. Houghton's apparatus includes a polypropylene mesh container, similar to a tea bag, which encloses reactive particles. The containers, however, are not amenable to general organic synthesis techniques. Further apparatuses are disclosed in German Published Patent Application Number DE 4005518 and European Patent Number 0355582, issued to Boehringer Ingelheim KG. Like the earlier devices, these apparatuses are not suitable for the synthesis of general organic compounds and are directed toward peptide or oligonucleotide synthesis. An approach describing the synthesis of unnatural, oligomeric peptides is reported by Simon et al. (*Proc. Natl. Acad. Sci. USA*, 1992, 89:9367).

The synthesis of general organic compounds poses many difficulties which are absent in the synthesis of peptides or oligonucleotides. Among the many special problems found in the synthesis of general organic compounds, as opposed to peptide or oligonucleotide synthesis, is the problem of providing a device which will accommodate the wider range of synthetic manipulations required for organic synthesis. The synthesis of organic compounds often

requires such varied conditions as use of an inert atmosphere, heating, cooling, agitation, or an environment to facilitate reflux. Such synthesis requires chemical compatibility between the materials used in the apparatus for multiple synthesis and the reactants and solvents. Consequently the apparatus must be constructed of materials which are resistant to organic synthesis conditions and techniques. Organic synthesis also often requires agitation. Such agitation may be accomplished by magnetic stirring, sonicating, or rotational shaking. None of the prior art devices are suitable for use under these special conditions required for general organic synthesis. Accordingly, none of the above-disclosed devices or methods for the multiple, simultaneous synthesis of peptides or oligonucleotides are useful for the synthesis of general organic compounds.

While undeniably useful, peptides or oligonucleotides have significant limitations in their application to pharmaceutical discovery programs. The chemical leads discovered from these collections of compounds require extensive modification due to the general unsuitability of peptides or nucleotides as stable, orally active drugs. The building blocks utilized are limited, even allowing for the use of unnatural enantiomers or artificial amino acids and modified nucleotides that are not found in nature. The peptides or oligonucleotides inherently possess a repetitive linkage, either an amide or a phosphate moiety, which limits their structural diversity.

Some of the problems associated with carrying out simultaneous organic chemical reactions in a single apparatus have been solved in the prior art, such as in Cody et al., U.S. Patent No. 5,324,483. This patent describes an apparatus and method which provide for multiple, simultaneous synthesis of organic compounds. The apparatus consists of a reservoir block having a plurality of wells; a plurality of reaction tubes, usually gas dispersion tubes, having filters on their lower ends; a holder block having a plurality of apertures; and a manifold, which may have ports to allow introduction or maintenance of a controlled environment. The manifold top wall has apertures and a detachable plate with identical apertures. The apparatus is constructed from materials which will accommodate heating, cooling, agitation, or corrosive reagents. Gaskets are placed between the components. Rods or clamps are provided for fastening the components together. Apparatus operation involves placing the filters on the lower ends of the reaction tubes in the reservoir block wells, with the upper ends passing through the holder block apertures and into the manifold. The apparatus is said to provide in excess of 1 mg of each product with structural knowledge and control over each compound. A series of building blocks are covalently attached to a solid support. These building blocks are then modified by covalently adding additional different building blocks or chemically modifying some existing functionality until the penultimate structure is achieved. This is then cleaved from the solid support by another chemical reaction into the solution within the well yielding an array of newly synthesized individual compounds, which after post-reaction modification, if necessary, are suitable for testing for activity.

However, as with the similar apparatuses designed specifically for use in the synthesis of peptides or oligonucleotides, the apparatus is designed for carrying out reactions on a solid phase. While solid-phase reactions are desirable under some circumstances, the apparatus described in Cody et al. requires a complex, non-disposable reaction vessel with a porous frit, which is not necessary for all chemical reactions and which adds to the expense of the overall apparatus. Furthermore, the manifold that encloses all of the reaction tubes at the same time makes it impossible to provide separate environments for reactions at the same time.

Accordingly, an apparatus in which chemical reactions, particularly those reactions common to synthetic organic chemistry such as reflux, can be carried out in simple reaction vessels is desirable. Particularly desirable, is an apparatus in which the reaction vessels are disposable commercially-available tubes that can be readily replaced so that the apparatus can be sequentially used with little delay between reactions.

SUMMARY OF THE INVENTION

Accordingly, it is an object of the invention to provide a modular apparatus having interchangeable parts in which a variety of different organic chemical reactions can be carried out in a collection of simple reaction vessels, either with or without the presence of a solid phase.

It is a further object of the invention to provide an apparatus in which simultaneous reactions can be carried out in disposable reaction vessels, such as simple straight-wall test tubes.

It is another object of the invention to provide an apparatus in which multiple reactions can be sampled independently during the simultaneous reactions with disturbing the integrity of the individual reaction environments.

It is yet another object of the invention to provide independent heating and cooling zones so as to allow reflux of individual reaction vessels in a modular apparatus.

It is a further object of the invention to provide simultaneous reactions in simple reaction vessels, such as glass test tubes, under pressure, vacuum or a selected gaseous environment.

It is a further object of the invention to provide an apparatus that is sufficiently flexible to allow use of more complicated reactions vessels, in addition to simple reaction vessels, simply by changing one or more of the interchangeable modules of the apparatus.

According to the invention, there is provided an apparatus for chemical synthesis, including a reaction block with an upper surface having an array of uniformly sized depressions in the surface, each depression having a fixed shape and area at the surface; and at least one function block having an upper surface and a lower surface, wherein the function block has a plurality of through passages from the function block upper surface to the function block lower surface arranged in an array to match the array in the reaction block, whereby the reaction block and the function block or blocks together form a collection of interior spaces in the apparatus, wherein the interior spaces are adapted to surround a corresponding collection of reaction vessels located in the depressions. One embodiment also includes an upper compression block and a connector means between the reaction block and the compression block, whereby the reaction block and the compression block can be drawn together with the function block interposed therebetween, such that the array of through passages in the function block matches the array of depressions in the reaction block. In another embodiment, the compression block is part of a function block. A preferred embodiment is an apparatus wherein the function block comprises a functional element that is (a) a through passageway having an entrance and an exit located in a side surface of the function block, (b) a through passageway having an inlet located in a side surface of the function block and a plurality of outlets located in an array that matches the array in the reaction block; (c) a heating or cooling element; (d) a groove on an upper or lower surface of the function block, the groove connecting the plurality of through passages; and (e) a passageway in a first function block that connects with a passageway in a second function block when the first function block and the

second function block are assembled, thereby forming a passageway that is continuous in adjacent function blocks. Preferably the apparatus comprises (1) a reaction block comprising (a) a heating element or (b) the second through passageway, (2) an insulating function block, (3) a cooling function block, comprising (a) a cooling element or (b) the second through passageway, (4) a gas manifold block, comprising (a) the second or third through passageway or (b) a combination of a sealing member and a function block having the groove in a surface that forms an internal passageway in combination with the sealing member, and (5) a compression block. In another embodiment, the function block further includes a through passageway having an entrance located in a side surface of the function block. In one embodiment, the function block also includes a groove or grooves located on an upper or lower surface of the function block, and preferably further comprises a sealing member, wherein the sealing member is located next to the groove on an upper or lower surface of the function block, and wherein the combination of the sealing member and the groove form at least one internal passageway in the apparatus. In a preferred embodiment, the reaction block or the compression block further includes at least one functional element comprising (a) a through passageway having an entrance and an exit located in a side surface of the block, (b) a through passageway having an inlet located in a side surface of the block and a plurality of outlets located in an array that matches the array in the reaction block, (c) a heating or cooling element, (d) a groove on an upper or lower surface of the block, the groove connecting the plurality of through passages, or (e) a passageway in the reaction block or the compression block that connects with a passageway in a function block when the reaction block or the compression block and the function block are assembled, thereby forming a passageway that is continuous in adjacent blocks. Preferably, the connector means indirectly connects the reaction block to the compression block via a further connector means attached to an intermediate function block. In one embodiment, the through passages are sized to closely fit the reaction vessels. In one embodiment, the collection of reaction vessels are straight-wall test tubes that closely fit the through passages when the reaction block and function block are assembled. Preferably, the reaction vessels are round-bottom, conical-bottom or flat-bottom test tubes. In another embodiment, the apparatus also includes at least one sealing member adapted to fit between a reaction block and a function block, between two function blocks, or between a function block and a compression block. Preferably, the sealing member comprises a continuous strip of compressible material at a perimeter formed between the reaction block and the function block, between two function blocks, or between the function block and the compression block. In another embodiment the compression block or a function block comprises a plurality of septum seals located in an array to match the array of the reaction block, and the apparatus further comprises a plurality of tubular inserts insertable into the plurality of septum seals, whereby the tubular inserts provide access to the interior spaces of the apparatus. Preferably, at least one of the tubular inserts comprises a porous frit insertable into one of the depressions or into a through passage of a function block. In one embodiment, the tubular insert extends beyond the porous frit. In one embodiment, the through passages of the function block have the fixed shape and area of the depressions at the reaction block upper surface. In another embodiment, the through passages of the function block also include chromatography columns adapted to fit into the through passages, filters adapted to fit into the through passages, or a combination of chromatography columns and filters adapted to fit into the through passages. In a preferred embodiment, the apparatus is present

as a kit that includes the reaction block, the compression block, the connector means, and a plurality of interchangeable function blocks. Preferably, the kit contains the plurality of interchangeable function blocks that include a plurality of functional elements, wherein a function block comprises at least one functional element.

BRIEF DESCRIPTION OF THE DRAWINGS

The invention will be better understood by reference to the following detailed description of specific embodiments, considered in combination with the drawings that form part of the specification.

FIG. 1 is a cross-sectional view of an assembled collection of modular blocks that form a first embodiment of an apparatus of the invention.

FIG. 2A is a top plan view of a first embodiment of a reaction block of the invention showing an array of depressions into which reaction vessels will fit.

FIG. 2B is a cross-sectional view taken along line A—A of FIG. 2A.

FIG. 2C and FIG. 2D are cross-sectional views of a portion (shown in the shadow-lined box) of the function block shown in FIG. 2B, showing conical bottom reaction chambers (FIG. 2C) and round bottom reaction chambers (FIG. 2D).

FIG. 3A is a top plan view of a first embodiment of an insulating function block of the invention.

FIG. 3B is a vertical cross-sectional view taken along line B—B of the embodiment of FIG. 3A.

FIG. 3C is a vertical cross-sectional view of another embodiment of an insulating block.

FIG. 4A is a top plan view of a first embodiment of a cooling function block of the invention.

FIG. 4B is a cross-sectional view taken along line B—B of FIG. 4A.

FIG. 4C is a front plan view of the embodiment of the invention shown in FIG. 4A and FIG. 4B.

FIG. 5 is a top plan view of a first embodiment of a sealing member of the invention.

FIG. 6 is a top plan view of a second embodiment of a sealing member of the invention.

FIG. 7A is a top plan view of a first embodiment of a function block that is a manifold or gas block showing a series of grooves in the top surface of the function block that connect through passages so as to provide, in combination with the sealing member of FIG. 5, a series of interior passageways leading into each of the through passages.

FIG. 7B is a cross-sectional view taken along line B—B of FIG. 7A.

FIG. 8 is a cross-sectional view of a portion of the embodiment of the invention shown in FIG. 1 showing two straight-wall test tubes located in the apparatus and a reflux reaction occurring in each of the tubes.

FIG. 9 is a cross-sectional view of a further embodiment of the invention showing a series of tubular inserts that provide access to each of the reaction vessels located in an apparatus of the invention.

FIG. 10A is a plan view of one side of an apparatus of the invention showing one embodiment of a connector means used to hold various parts of the apparatus together.

FIG. 10B is a side view at ninety degrees from the apparatus shown in FIG. 10A, which shows side views of two connector means used in the embodiment of the invention shown in FIG. 10A.

FIGS. 11A to 11C are a series of cross-sectional views of different embodiments of the gas block of FIG. 7.

FIGS. 12A to 12D are a series of cross-sectional views of a number of alternative embodiments of a function block useful with individual column chromatography or filtering elements.

FIGS. 13A to 13C are a series of cross-sectional views of a number of alternative embodiments of a function block having internal filtering elements.

The invention now being generally described, the same would be better understood by reference to the following specific embodiments of the invention, which are not to be considered limiting of the invention defined by the claims.

DESCRIPTION OF SPECIFIC EMBODIMENTS

Reference will now be made in detail to a number of embodiments of the invention. When reference is made to figures, the same reference numbers are used throughout to refer to the same parts of the apparatus.

The apparatus of the invention comprises a series of stackable blocks that contain, when assembled, an array of individual interior chambers that closely fit around reaction vessels in which chemical reactions typical of organic synthesis can take place separately from each other. By forming individual chambers that surround the individual reaction chambers, reactions can occur independently of each other with a minimum chance of cross-contamination. In preferred embodiments, the apparatus allows for the use of simple, disposable, reaction vessels. In one preferred embodiment, the reaction vessel is a simple straight-wall test tube. Such test tubes are made by a number of manufacturers throughout the world to common specifications for interchangeability and are thus commercially available in standard sizes. A commercially available test tube (or other reaction vessel) is considered to be one that is manufactured by an independent manufacturer not associated with a manufacturer of the apparatus of the invention and advertised for sale for any purpose other than for use in an apparatus of the invention, even if also so advertised. If desired, a reaction vessel to be enclosed in an apparatus of the invention can be made in a size different from those normally available commercially. Examples of standard test tube sizes that can be used in an apparatus of the invention include (I.D. and length, all measured in mm) 6 x 50, 10 x 44, 10 x 50, 10 x 65, 10 x 75, 12 x 75, 13 x 100, 15 x 85, 15 x 125, 16 x 100, 16 x 125, 16 x 150, 17 x 100, 17 x 120, 18 x 150, 20 x 125, 20 x 150, 22 x 175, 25 x 150, 25 x 200, and 25 x 250. Of these the first seven are the most commonly used sizes, with the 10 x 75 mm test tubes being especially preferred. It should be readily recognized that the reaction vessel is not an essential part of an apparatus of the invention (unless specially prepared for use in the apparatus), but is generally a disposable item that will be inserted into the apparatus. However, in some embodiments, such as when a reaction or other function block (see below) is formed from an inert material such as polytetrafluoroethylene, the sides of the reaction vessel can be formed entirely or in part from the reaction block or other function block itself.

It will be appreciated by those skilled in the art that the apparatus of the present invention that readily accepts commercially available, and preferably disposable, test tubes as the reaction vessels provides advantages over prior art devices in which reaction vessels are reused. That is, disposable reaction vessels can be used for a single

set of syntheses, and then replaced with a new, clean reaction vessels for a subsequent syntheses in the same apparatus, without having to clean the reaction vessels before the next set of syntheses are performed. Therefore, there is little loss of time between subsequent syntheses and the potential of cross-contamination between one set of syntheses and a subsequent set of syntheses is minimized. Moreover, use of commercially available disposable test tubes in the apparatus minimizes the costs of replacing the reaction vessels.

The apparatus of the invention comprises a collection of blocks that are capable of carrying out a variety of different functions and that are therefore referred to herein as "function blocks." The blocks are designed to be interchangeable, so that a series of different chemical reactions can be carried out in the reaction vessels (which are themselves interchangeable) simply by disconnecting the modular blocks and replacing one or more of the modular blocks with another. For example, a modular unit containing a heating element can be used as a bottom or first block of a reaction stack. An insulating block can be placed on top of the first block to separate the heating function from a cooling function that is present in the next cooling block that is placed on top of the insulating block. A manifold or gas block can be placed on top of the cooling block, and a compression plate or block can be placed on top to form a multilayer, sandwich-like apparatus that is held together by a connector means between the uppermost and lowermost blocks or surrounding the blocks. After carrying out a reflux reaction in such an assembly of reaction blocks, the upper three or four blocks can be removed and replaced by a function block that provides, for example, stirring of the individual samples in a solvent at room temperature (for example, by bubbling a gas through the solvent using a hollow tube inserted into the solvent).

Generally, the individual function blocks are aligned using registration pegs and holes in the various blocks to allow easy fitting between blocks so that the through passages in which a reaction vessel, such as a test tube, will be inserted can be easily aligned. Other alignment techniques include a base plate with two or more vertical rods and corresponding holes in each of the function blocks. Other ways of registering the various function blocks with each other are possible as is well known in the art; registration of different functional blocks with each other is not a specific part of the present invention.

Separate modular blocks can be provided to allow for reflux, cooling, heating, shaking, sonication, vibration, pressurizing, drawing a vacuum, filtering, sample withdrawal, and the like. Sealing members can be provided between various layers of the apparatus to allow the interior of the apparatus to be isolated from the atmosphere. The resulting apparatus is very compact and yet capable of providing for a large number of independent reactions in a small space. For example, a series of 96 reflux reactions can be carried out in a space not much larger than a test tube rack approximately 7.6 cm high. Possibility of cross-contamination is reduced by the simple expediency of providing disposable reaction vessels, as well as by other features of the apparatus of the invention, such as efficient cooling which prevents solvent from escaping the reaction vessels and condensing in inappropriate locations of the apparatus, providing small passageways for gas access to the individual reaction vessels rather than a single open space, and other design features that will be apparent from the discussions of individual function blocks.

Although the function blocks are generally described below as being placed above or below each other (referred to as vertical stacking), it is apparent that other physical arrangements are possible. For example, under

certain circumstances it may be desirable to use "partial blocks," i.e., ones that do not fully cover the function block immediately below but which operate side by side to provide different functions in the same horizontal section of a vertical stack of reaction blocks. For example, two partial function blocks that provide a gas to the reactions vessels can be provided side by side, each block providing a 6 × 8 array of gas inlets to half of the reaction vessels present in a 12 × 8 vessel reaction block, in order that two different gaseous reaction environments can be provided at the same time, each gaseous environment being provided to half of the reaction vessels (i.e., one gaseous environment provided by one of the partial blocks, and another gaseous environment provided by the second partial block). Alternatively, insulating blocks can be provided that surround the main reaction stack and isolate the sides of the reaction stack from the external environment.

In describing some of the function blocks, the blocks will be given a name to designate one use that can be made of them (such as a "cooling function block") to avoid the necessity of awkward or nondescriptive language (such as "first function block" and "second function block"). The use of a descriptive name is not to be considered limiting, because the individual function blocks can be used for different functions depending, for example, on what is circulated through them from outside the apparatus. For example, the "cooling function block" described below contains an internal passageway through which a cooling liquid can be circulated to cool that portion of the reaction vessel that passes through the "cooling block." However, a user could equally well circulate a heated liquid through the same block, or could merely use the block as a spacer if no heating or cooling is needed for a particular step. Accordingly, the use of a descriptive term to name a function block does not limit the uses to which that block can be applied, unless the block is specifically stated to be so limited or is so limited at a given time by the manner in which it is used.

Referring to the figures that show various embodiments of the invention, FIG. 1 shows a cross-sectional view of the first embodiment of the invention, in which the apparatus 10 is formed from a series of interchangeable block-like modules. In the embodiment shown in FIG. 1, the lowermost module is a reaction block 100 into which the lower end of a reaction vessel 500 (e.g., a standard 10 mm x 75 mm round bottom test tube) fits. The apparatus 10 is assembled in layers with the next layer being a sealing member 430, which will be discussed in detail later, as will all other modules shown in this initial cross-sectional view. Sealing member 430 is followed by an insulation block 310, a second sealing member 430, a cooling block 320, another sealing member 430, a gas manifold block 330, which functions in combination with a different sealing member 420, and a final compression block 200. In all cases, the depressions in reaction block 100 and the through passages in the other modular function blocks of the apparatus of the invention align with one another to form an array of interior spaces that closely fit the test tubes or other reaction vessels 500 selected to fit therein. Such a close fit allows for better heat transfer or other performance of the function being carried out by a function block. By "closely fit" is meant that a gap of no more than 5 mm, preferably not more than 0.25 mm, and more preferably no more than 0.15 mm is present in the apparatus. Naturally, the size of the gap depends in part on the precision of manufacture of the reaction vessels and on the relative coefficients of expansions of the materials used to make the reaction vessels and the apparatus, because the apparatus is designed to use interchangeable reaction vessels in each of the reaction

locations of the apparatus. A gap as small as 0.01 mm is sufficient for a precisely manufactured collection of reaction vessels, unless the coefficients of expansion of the apparatus and the reaction vessel are sufficiently different to require more expansion room for the particular temperature range to be used in the apparatus. Even for less precisely manufactured reaction vessels, the diameter of the passageway is no more than 0.1 mm, preferably no more than 0.05 mm, and even more preferably no more than 0.01 mm, larger than the expected largest diameter of the reaction vessels, according to the manufacturing specifications of the reaction vessel. For example, if the test tubes are manufactured (and selected by the manufacturer, if necessary, before shipping) to be 10.00 $\pm$ 0.02 mm in diameter, a diameter of 10.03 mm can be selected for a given through passageway that will contain the test tube.

FIG. 2A is a plan view of the bottom reaction block 100 shown in FIG. 1. The phrase "reaction block" is not intended to indicate that reaction can occur only in the region formed by the depressions 101 in the top surface 102 of the reaction block. However, because most organic reactions occur in an organic or aqueous solvent and because depressions 101 form the bottom part of the interior chambers into which reaction vessels (such as reaction vessels 500 of FIG. 1) will be inserted, reaction will typically take place at least in the region formed by depressions 101. As will be discussed later for FIG. 8, solvent may be present in a reaction vessel above the upper surface 102 of reaction block 100, in which case reaction will also occur in such other regions.

Depressions 101 are formed to closely fit the bottom portion of the reaction vessel 500 for which the individual apparatus is designed. As shown in FIGS. 2B to 2D, which is a cross-section taken along line A—A of FIG. 2A, a depression can be formed to conform to the flat bottom 103 (shown in FIG. 2B), conical bottom 104 (shown in FIG. 2C) or round bottom 109 (shown in FIG. 2D) of a test tube. It will be understood that other vessel shapes can be similarly accommodated by the depressions.

Guide pegs 106 are shown both in FIG. 2A and FIG. 2B. These guide pegs function together with guide holes in other modular units so that the array of depressions 101 in reaction block 100 will be aligned with through passages in other modules. The reaction block 100 may include one or more guide holes 107 which can receive interengaging pegs 105 to attach the block 100 to a support surface (not shown). An optional internal heating element 108 is shown in FIGS. 2B to 2D.

The arrays of depressions 101 shown in FIG. 2A is an 8 $\times$ 12 array, providing space for 96 reaction vessels. Other numbers of depressions can be used (for example, a 6 $\times$ 8 array of 48 reaction vessels), and the array can be present in a different pattern (such as a circular or spiral array) or even no pattern (i.e., irregular or random). As will be apparent from discussion of other modules, the form of the array is not essential, because it is merely necessary that the array used in each module match the array used in other modules. Likewise, the rectangular form of reaction block 100 is not essential, as each reaction block can be likewise be formed in different horizontal cross sections, such as squares, circles, or ovals. Additionally, the upper and lower surfaces of the individual reaction blocks need not be planar, because it is only necessary that they fit together. However, planar upper and lower surfaces are preferred for ease of handling, interchangeability, and assembly.

"Upper," "lower," "side," and similar expressions refer to the orientation of the apparatus as a whole or to the various blocks in their normal operating positions. In FIG. 1 and FIG. 8, for example, the top of the FIG. is the top of the apparatus as it would normally be placed in operation.

FIG. 3A is a plan view of a first embodiment of an insulating function block 310 of the invention. Function block 310 is formed from perimeter portion 312 which forms a continuous border, preferably of about 1 cm wide, around the perimeter that is formed between adjacent function blocks. Void space 314 is present in the interior portion of function block 310 to allow passage of reaction vessels between blocks without interference and to provide an insulating air space. Guide holes 120 and pegs 106 are present near the corners of insulating function block 310 and elsewhere in the perimeter portion 312 for easy alignment of the different blocks of the apparatus. A vertical cross section of the embodiment of FIG. 3A taken along the line B—B is shown in FIG. 3B.

As alternatives to the embodiment of the insulating block shown in FIGS. 3A and 3B, other embodiments of insulating function blocks can be used. For example, as shown in FIG. 3C, a simple solid block having through passageways 301 as in other function blocks can serve as an insulating block. Such an insulating block would be made from an insulating material, typically one with a coefficient of heat transfer of less than 10 Watts/(m)(°C), preferably less than 1 Watt/(m)(°C), and more preferably less than 0.22 Watt/(m)(°C). Typical materials out of which the insulating block can be constructed include Ultem™, polyethersulfone resin, and polycarbonate resin. Alternatively, the interior space 314 of the embodiment shown in FIGS. 3A and 3B can contain an insulating material with an array of through passages. Suitable insulating material is, for example, fiberglass in the form of a mat to avoid heat transfer by convection, aerogel silica (opacified), which has a coefficient of heat transfer of about 0.013 Btu/(h)(ft^2)(°F/ft), and the like. In all cases the exterior portion (perimeter) 312 of insulating block 310 is made from a mechanically sound material, such as PTFE, to provide rigidity to the insulating block as a whole, because compression forces used to hold the apparatus together are generally provided at the exterior surfaces of the apparatus.

FIG. 4A is a plan view of a first embodiment of a different function block of the invention, usually referred to as a cooling or heat-transfer block. Function block 320, as shown in this embodiment of the invention, is normally used for heating or cooling as it is designed to allow for passage of a fluid through the interior of the function block and between the through passages 301 through which the reaction vessel will be inserted. The function block 320 contains a continuous fluid through passageway 321, best seen in the cross-sectional view of FIG. 4B, which is taken along line B—B of FIG. 4A. As seen in FIG. 4B, multiple holes 322 have been drilled in function block 320 and then selectively sealed by a series of plugs 327 to provide a continuous fluid passageway 321 throughout the interior of function block 320. As shown in FIG. 4C, a fluid entrance 323 is provided, typically via a larger hole to provide access to multiple smaller fluid passageways 321. Fluid then is collected and exits through a larger fluid passageway and through fluid exit 325. Thus, either a hot or a cold liquid can be circulated through function block 320 in order to either heat or cool the reaction vessel where it contacts or closely approaches the walls of through passages 301.

FIG. 4C is a side view of the cooling/heating block 320 shown in FIG. 4A and 4B in which fluid entrance 323 and fluid exit 325 are visible on a side of the apparatus to provide access for fluid transfer. Also shown are guide pegs 106 which are used for aligning through passages 301 with the next modular block.

For effective heat transfer, heating/cooling block 320 is typically formed from a material with a low heat capacity, typically a metal. Preferred heat-transfer materials are copper and aluminum, which can be coated or plated for corrosion resistance (e.g., with a nickel-chromium alloy plating).

FIG. 5 and FIG. 6 show first and second embodiments of a sealing member of the invention. FIG. 5 shows a full sealing member 420, which consists essentially of a solid gasket or septa having locator holes 408 for cooperating with guide pegs. Preferably, the sealing member is a rectangle, most preferably a rectangle having dimensions 16.26 cm × 20.32 cm × 0.15 mm, with the locator holes 408 being about 0.5 to 1 cm in diameter. FIG. 6 shows an array sealing member 430 which contains an array of through passages 431 to allow reaction vessels to pass through the sealing member 430. Preferably, the array sealing member 430 is a rectangle, most preferably a rectangle having dimensions 16.26 cm × 20.32 cm × 0.15 mm, with the locator holes 408 being about 0.5 to 1 cm in diameter, and the array of through passages are arranged as an 8 × 12 array of about 1 cm diameter holes, although it will be understood that other diameter holes and any of the potential arrays of reaction vessels described can be used to form the array of the sealing member. As is apparent, full sealing member 420 is not present at a central location in the apparatus but, instead, is used at an end of the apparatus as will be discussed later. The sealing members 420, 430 are formed from a material appropriate to the sealing function and to the reaction that will be carried out in the apparatus of the invention. Most sealing members are at least somewhat compressible and are made from or coated with a material that will resist organic chemicals, particularly the solvents that will be used in the apparatus. A preferred gasket material is polytetrafluoroethylene (PTFE)-coated fluorosilica rubber sheet of about 0.5 to 2.0 mm thickness, preferably 1.5 mm thickness, such as that manufactured by Specialty Silicone Products and many other manufacturers. Such a material allows a wide variety of reactive materials to be used in the apparatus of the invention without concern for gasket deterioration. This material is particularly preferred for a full sealing member 420 when the reactions are expected to yield corrosive solvent vapors, as such vapors are concentrated in the upper regions of the apparatus. In other embodiments, a PTFE or other corrosion-resistant coating may be less preferred in view of the fact that a better seal can be achieved without such coating. Thus, for example, the array sealing member 430 is preferably made of a resilient compressible material that lacks a PTFE coating in order to ensure an optimal seal. Alternatively, a connector means (discussed below) providing more robust compression can be employed to compensate for any reduction in sealing capacity of sealing member 420, 430 due to such coating. In some embodiments, particularly those not involving corrosive solvents or vapors, such corrosion-resistant coating can be omitted. Other sealing members, such as one which just forms a perimeter seal at the outer edge of adjacent function blocks, are also useful with this apparatus.

FIG. 7A is a plan view of a function block 330 of the invention that typically is used as a gas block or manifold for providing access of, for example, an inert atmosphere to the top of each of the reaction vessels. As shown in FIG. 1, gas block 330 is generally used in combination with a full sealing member 420, as shown in FIG.

5A. Referring to FIGS. 7A and 7B, visible in the top surface 332 of gas block 330 are a series of grooves 331. When a full sealing member 420 (not shown) is placed on top of gas block 330, the grooves 331, top surface 332 of block 330, and bottom surface of full sealing member 420 form the walls of a series of interior passageways 334 that conduct gas or fluid into the interior of gas block 330 through fluid inlet 333. The gas or other fluid has access to each of the through passages 301 to provide access of the fluid to the interior space formed by the through passages 301 and thus to the top (as will be shown later) of the individual reaction vessels.

The function of the grooves 331 in forming passageways 334 is readily apparent from FIG. 7B, which is a cross-sectional view taken along line B—B of FIG. 7A. As can be seen in this cross-sectional view, the grooves 331 will form an interior passageway once a sealing member 420 (not shown) has been placed on top of the grooved upper face 332 of gas block 330.

FIG. 8 shows an apparatus 10 of the invention in cross-section during operation. The apparatus 10 is formed from the same series of modular blocks shown in FIG. 1. The bottom block is reaction block 100, followed in turn by insulating block 310, cooling block 320, gas manifold block 330, and compression block 200. Sealing members 430 separate the reaction block 100, the insulating block 310 and the manifold block 330; sealing member 420 separates the manifold block 330 and the compression block 200.

Compression block 200 is not mechanically constrained and can be either solid or can have through apertures 201, as shown in FIG. 8, which can be used to provide access to the interior of reaction vessels 500, as described later. Because the apertures 201 of the compression block 200 do not have to allow passage of reaction vessels 500, they can be, and preferably are, smaller that the cross-sectional area of the reaction vessels. The compression block 200 can be provided as a separate module, as shown, or can be present as part of a function block. Any of the function blocks described herein can act as a compression block if provided with a connector means as described below.

In operation, a solvent 110 is provided in the lower portion of reaction vessel 500. Heat is provided by reaction block 100 (e.g., to heat the solvent to about 100-150°C), which can contain an electrically powered heating element or can simply be formed from metal with good heat conductivity which is placed on a hot plate (not shown). Solvent evaporates as shown by solvent vapor lines 112, recondenses on the walls of reaction vessel 500, and flows back (114) into the boiling solvent 110, in the typical manner of a reflux reaction. Cooling block 320 provides continuous cooling (e.g., to about 0-5°C) and thus provides for condensation of solvent by continuous circulation of a cold fluid through interior passageways 321 in cooling block 320 between through passageways 301. Nitrogen gas (e.g., at about 1 atm) is provided in this embodiment through the gas block 330 through the passageways formed by the combination of the gas block 330, the function block 320 and the sealing member 420, as described earlier for FIGS. 7A and 7B for the embodiment in which the gas block contains grooves in its surface. An array sealing member 430 is interposed between the gas block 330 and the adjacent function block 320 in this embodiment to allow passage of the gas into the through passages of the apparatus.

FIG. 9 shows another embodiment of the invention in which access is provided into the interior of reaction vessels 500 through a series of septum seals 221, in this embodiment located in access holes 201 of compression

block 200. Insert tube 601 is shown in the form of a hollow tube which comprises a porous frit 602 located near the bottom 603 of insert tube 601. Porous frit 602 can be used to add or withdraw fluids present in the bottom of the reaction vessels 500. As shown in FIG. 9, frits 602 are not located at the bottom of insert tube 601, but a short distance above the bottom. However, in other embodiments it may be desired to locate the frit at the bottom of the insert 601 and to conform the shape of the frit 602 to the bottom shape of the reaction vessel 500 in order that liquid can be substantially or completely removed from the bottom of the reaction vessel 500. Selection of either design will depend on the intended use of the reaction vessel and can readily be made by a user skilled in the art, although alternative insert tubes 601 of either design can be provided with the apparatus. Additionally, a simpler insert tube (such as a hollow needle with no frit) can be provided for other embodiments.

A collection of insert tubes 601, one for each reaction vessel 500, can be provided in an array spaced in the same manner as the arrays of through passages, and the array can be maintained by a function block 600 that is either attached to or separate from the remainder of the apparatus 10. As shown in FIG. 9, function block 600 is separate from the main part of the apparatus 10 so that the insert tubes 601 may be raised and lowered to above and below the surface of a solvent that is present in the bottom of reaction tubes 500. Thus, insert tubes 601 can be used to withdraw (or add) liquid solvent from the bottom of reaction vessels 500 and can then be withdrawn to the upper portion of gas manifold block 330, which will be above the level of refluxing solvent.

FIG. 10A is a plan view showing a first embodiment of a connector means 800 that can be used with the embodiment of the invention shown in FIG. 1. A side view of the connector means 800 is presented in FIG. 10B. The connectors shown are conventional, commercially available connectors used to hold parts of an apparatus together (such a container and its lid) but are not intended to be limiting on the connector means that can be used. Instead, any other connector means can be employed to hold together the parts when a reaction is to be carried out under internal pressure. One known connector means, shown in FIGS. 10A and 10B, is a conventional snap-fit clamp with a lever 805 attached to one function block that snaps down to exert pressure on a flange 810 attached to another function block via a pressure bar 815 that engages a head 811 with the flange 815 to exert pressure. Connector means are preferably provided on the apparatus because the end user may decide to carry out a reaction under pressure. However, connector means are not required for an apparatus that will not be used under conditions of positive internal pressure.

The apparatus and the individual function blocks are not limited to the specific embodiments shown, but are only limited by the claims set out below. Other designs for interchangeable function blocks will be readily apparent to those of ordinary skill in the art now that the basic design of an apparatus of the invention has been set forth.

As nonlimiting examples, FIGS. 11 and 12 show alternative function blocks. FIG 11A shows a cross-sectional view of an alternative gas block or manifold compared to the embodiment shown in FIG. 7. The function block of FIG. 11A provides gas access to the interior through an inlet 323 leading to passageways 301 that are provided by a series of interconnected internal passageways 331 that are located entirely within the function block 330 rather than being formed on its upper surface 332. The detail of the gas block shown in FIG. 11B illustrates

a cross-sectional view of an upper portion of the alternative embodiment, illustrated in FIG. 7, in which the passageways 301 are formed as indentations or grooves 331A on its upper surface 332. FIG. 11C shows another alternative embodiment in which a gaseous atmosphere is directed to individual through passageways 301 by gas lines 335 and plugs 336 which fit into the upper apertures 337 of the through passageways 301. This embodiment is particularly useful if different gases are to be directed into different reaction vessels.

FIG. 12A shows a cross-sectional view of a function block 360 that can be used to collect material from or add material to the individual reaction vessels in combination with a chromatography, filtering or separating operation. The function or adaptor block 360 has a series of through passageways 301. A series of chromatography columns 362 that are adapted to fit into the top apertures 302 of the through passageways 301, while a series of filters 364 are adapted to fit into the bottom apertures 303 of the through passageways. Either a chromatograph column or a filter can be used individually or they can be used together as shown in FIG. 12A. FIGS. 12B to 12D show cross-sectional views of the upper portion (shown in the shadowlined box of FIG. 12A) of a series of alternative filter blocks. The connections between the columns and/or filters and the function block can be either press fits, as shown in FIG. 12A, or a threaded screw 304 as shown in FIG. 12B or other types of conventional fittings. Either male or female fittings are appropriate, and the fittings 305 can be formed as part of the function block, as shown in FIG. 12C, or can be formed from an insert 306 that is attached to the function block, as shown in FIG. 12D.

FIGS. 13A to 13C show a series of cross-sectional views of an alternative function block 370 for filtering, using filters 372 internal to the block. A filter 372 is inserted into the through passageway 301 via the upper aperture 302 and can be held in place by a variety of means. A preferred embodiment is shown in which the filter is simply press-fitted into the passageway 301 until it rests on a shoulder 307 formed between a wider portion 308 and a narrower portion 309 of the passageway 301. The filter 372 is shown by the series of short vertical lines. This press-fitting embodiment allows easy removal of the filter 372 for replacement or cleaning. FIG. 13B shows an expanded view of such a filter placement, in which only a portion of the function block 370 contained within the shadowlined box of FIG. 13A is illustrated. FIG. 13C shows a portion of an alternative embodiment in which a tube drain 311 is inserted in the function block 370 to allow liquid to remain in the passageway 301 until it is forced through the filter 372 by pressure or suction. The tube drain 311 is preferably a flexible tube that is inserted into an expelling chamber 350 to hold the tube drain 311 in proper position and also to serve as a conduit for directing material from the tube drain 311 into the next appropriate location. For example, the expelling chamber 350 can be positioned over a container to accept waste material when the liquid forced or withdrawn through the tube drain is waste material. Alternatively, the expelling chamber 350 may be positioned over another through passage (not shown) to direct the expelled liquid into another reaction vessel (not shown) when the filtrate is a desired intermediate product. The expelling chamber 350 is preferably a tube that can be releasably engaged with the tube drain 311 to hold it in place when needed but to allow easy removal for replacement or cleaning. For example, the expelling chamber 350 may be a tube with a partial slit in the length of the tube to told the flexible tube drain in the slit portion.

Numerous reactions can be carried out in an apparatus of the invention. The apparatus is not limited to any particular reaction, but is designed so that many different reactions can be carried out in a simple, preferably disposable, reaction vessel that can be purchased elsewhere and inserted into the various cavities in the interior of the apparatus. Examples of the kinds of chemical reactions that can be carried out in an apparatus of the invention are set forth in U.S. Patent 5,324,483.

It will be apparent to one of ordinary skill in the art that many changes and modifications can be made to the invention described herein without departing from the spirit or scope of the invention described in the claims that follow.

WHAT IS CLAIMED IS:

1. An apparatus for chemical synthesis, comprising:

a reaction block with an upper surface having an array of uniformly sized depressions in said surface, each depression having a fixed shape and area at said surface; and

at least one function block having an upper surface and a lower surface, wherein said function block has a plurality of through passages from said function block upper surface to said function block lower surface arranged in an array to match said array in said reaction block, whereby said reaction block and said function block or blocks together form a collection of interior spaces in said apparatus, wherein said interior spaces are adapted to surround a corresponding collection of reaction vessels located in said depressions.

2. The apparatus of claim 1, further comprising an upper compression block and a connector means between said reaction block and said compression block, whereby said reaction block and said compression block can be drawn together with said function block interposed therebetween, such that said array of through passages in said function block matches said array of depressions in said reaction block.

3. The apparatus of claim 1, wherein said compression block is part of a function block.

4. The apparatus of claim 1, wherein said function block comprises a functional element comprising: (a) a through passageway having an entrance and an exit located in a side surface of said function block; (b) a through passageway having an inlet located in a side surface of said function block and a plurality of outlets located in an array that matches said array in said reaction block; (c) a heating or cooling element; (d) a groove on an upper or lower surface of said function block, said groove connecting said plurality of through passages; or (e) a passageway in a first function block that connects with a passageway in a second function block when said first function block and said second function block are assembled, thereby forming a passageway that is continuous in adjacent function blocks.

5. The apparatus of claim 4, wherein said apparatus comprises (1) a reaction block comprising (a) a heating element or (b) said second through passageway; (2) an insulating function block; (3) a cooling function block, comprising (a) a cooling element or (b) said second through passageway; (4) a gas manifold block, comprising (a) said second or third through passageway or (b) a combination of a sealing member and a function block having said groove in a surface that forms an internal passageway in combination with said sealing member; and (5) a compression block.

6. The apparatus of claim 1, wherein said function block further comprises a through passageway having an entrance located in a side surface of said function block.

7. The apparatus of claim 1, wherein said function block further comprises a groove or grooves located on an upper or lower surface of said function block.

8. The apparatus of claim 7, further comprising a sealing member, wherein said sealing member is located next to said groove on an upper or lower surface of said function block, and wherein the combination of said sealing member and said groove form at least one internal passageway in said apparatus.

9. The apparatus of claim 2, wherein said reaction block or said compression block comprises at least one functional element comprising: (a) a through passageway having an entrance and an exit located in a side surface of said block; (b) a through passageway having an inlet located in a side surface of said block and a plurality of outlets located in an array that matches said array in said reaction block; (c) a heating or cooling element; (d) a groove on an upper or lower surface of said block, said groove connecting said plurality of through passages; or (e) a passageway in said reaction block or said compression block that connects with a passageway in a function block when said reaction block or said compression block and said function block are assembled, thereby forming a passageway that is continuous in adjacent blocks.

10. The apparatus of claim 2, wherein said connector means indirectly connects said reaction block to said compression block via a further connector means attached to an intermediate function block.

11. The apparatus of claim 1, wherein said through passages are sized to closely fit said reaction vessels.

12. The apparatus of claim 11, wherein said collection of reaction vessels are straight-wall test tubes that closely fit said through passages when said reaction block and function block are assembled.

13. The apparatus of claim 12, wherein said reaction vessels are round-bottom, conical-bottom or flat-bottom test tubes.

14. The apparatus of claim 2, wherein said apparatus further comprises at least one sealing member adapted to fit between a reaction block and a function block, between two function blocks, or between a function block and a compression block.

15. The apparatus of claim 14, wherein said sealing member comprises a continuous strip of compressible material at a perimeter formed between said reaction block and said function block, between two function blocks, or between said function block and said compression block.

16. The apparatus of claim 2, wherein said compression block or a function block comprises a plurality of septum seals located in an array to match said array of said reaction block, and said apparatus further comprises a plurality of tubular inserts insertable into said plurality of septum seals, whereby said tubular inserts provide access to said interior spaces of said apparatus.

17. The apparatus of claim 16, wherein at least one of said tubular inserts comprises a porous frit insertable into one of said depressions or into a through passage of a function block.

18. The apparatus of claim 17, wherein said tubular insert extends beyond said porous frit.

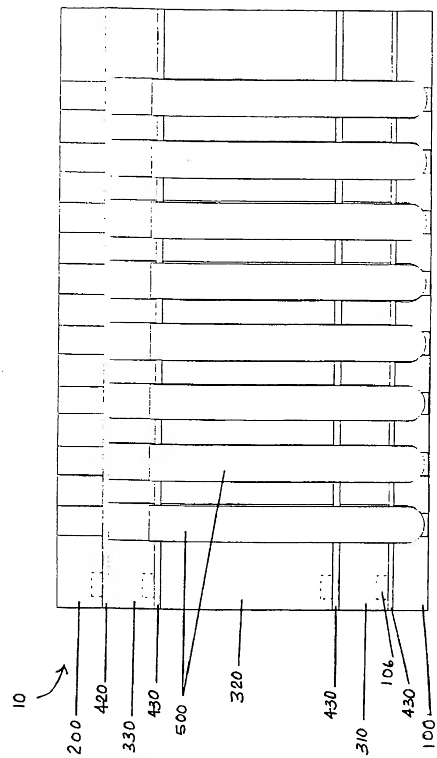
19. The apparatus of claim 1, wherein said through passages of said function block have said fixed shape and area of said depressions at said reaction block upper surface.

20. The apparatus of claim 1, wherein said through passages of said function block further comprise chromatography columns adapted to fit into said through passages, filters adapted to fit into said through passages, or a combination of chromatography columns and filters adapted to fit into said through passages.

21. The apparatus of claim 2, wherein said apparatus is present as a kit comprising: said reaction block, said compression block, said connector means, and a plurality of interchangeable function blocks.

22. The kit of claim 21, wherein the plurality of interchangeable function blocks comprise a plurality of functional elements, and wherein a function block comprises at least one functional element.

FIG. 1



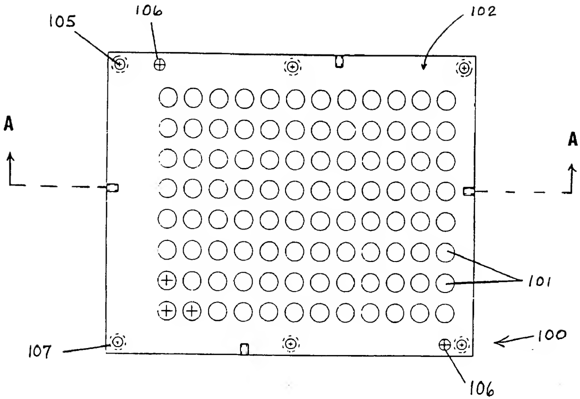


FIG. 2A

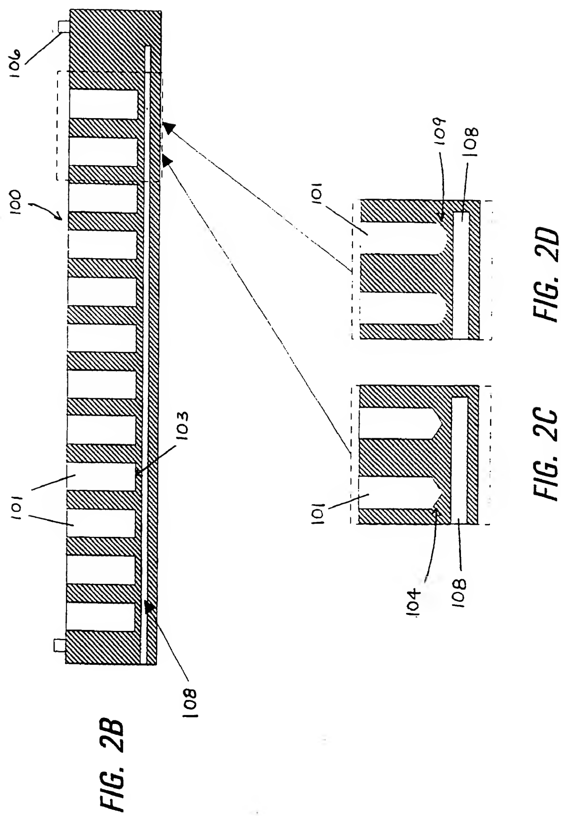
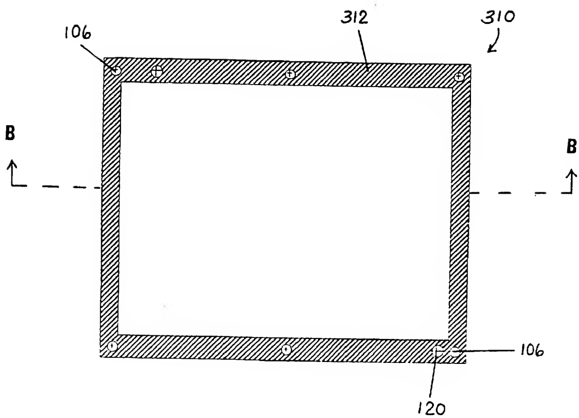


FIG. 2B

FIG. 2C

FIG. 2D

FIG. 3A



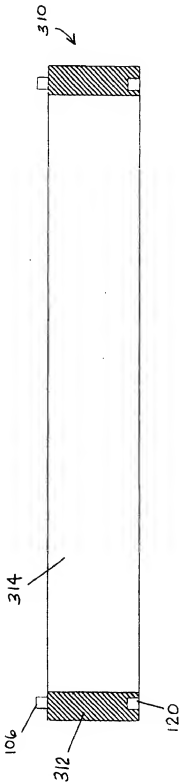


FIG. 3B

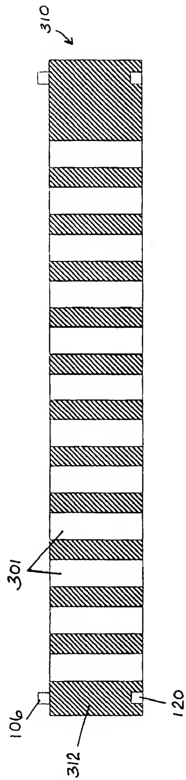


FIG. 3C

FIG. 4A

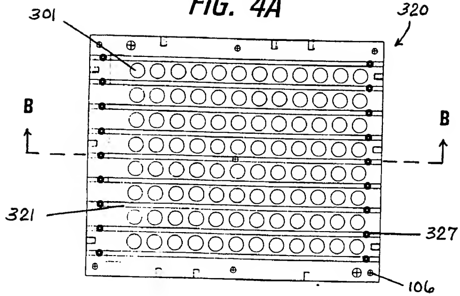


FIG. 4B

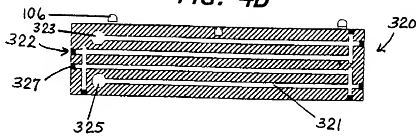
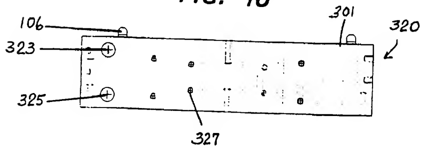


FIG. 4C



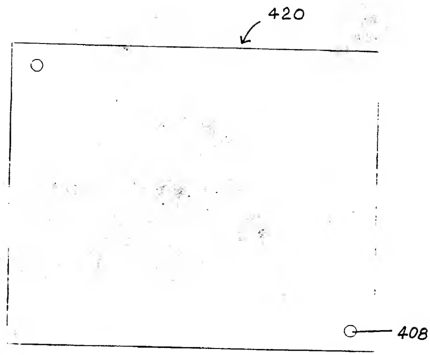


FIG. 5

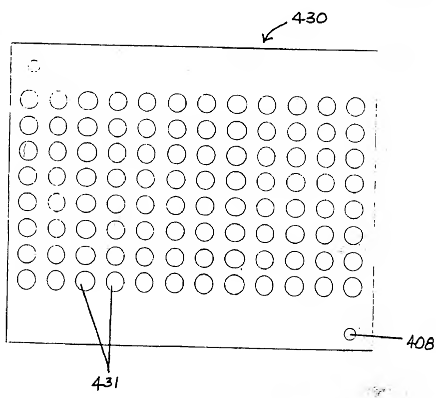


FIG. 6

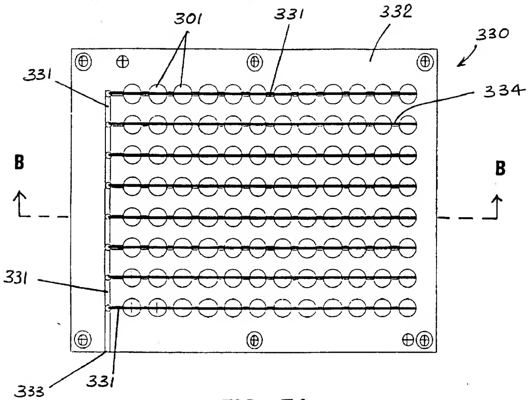


FIG. 7A

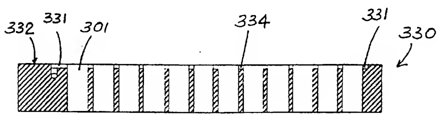


FIG. 7B

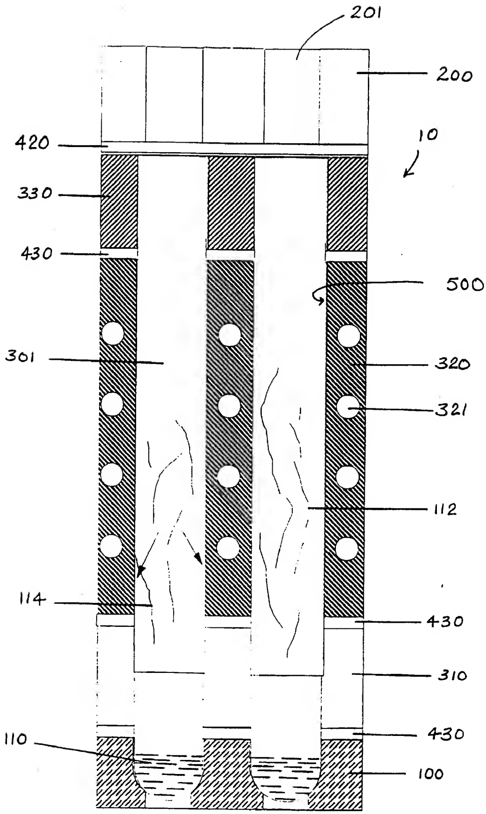

201
200
10
420
330
430
500
301
320
321
112
114
430
310
430
110
100

FIG. 8

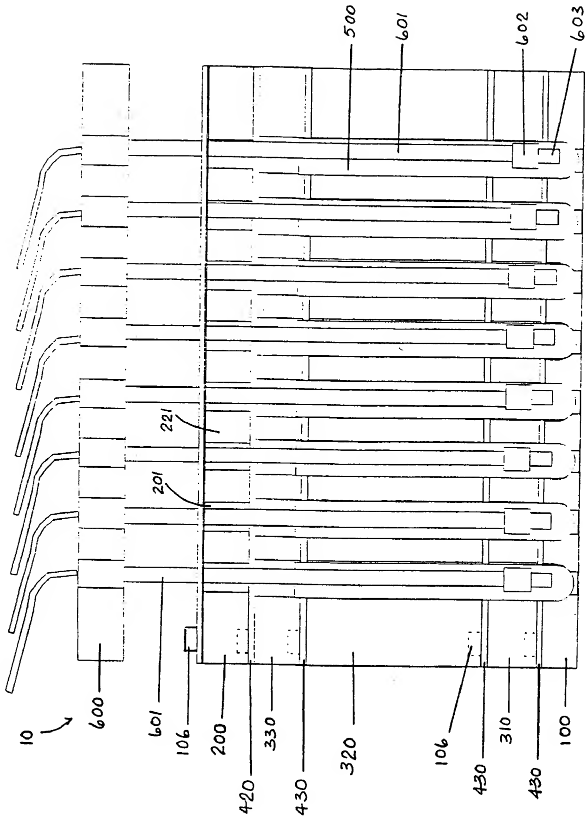

500
601
602
603
221
201
10
600
601
106
200
420
330
430
320
106
430
310
430
100

FIG. 9

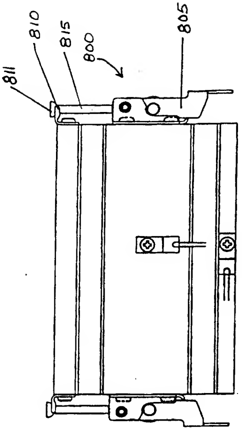


FIG. 10B

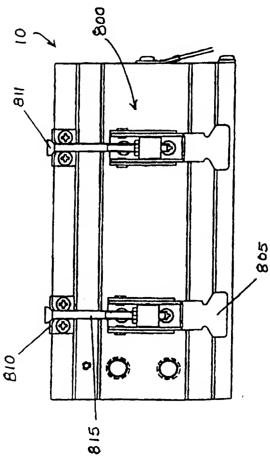


FIG. 10A

FIG. 11A

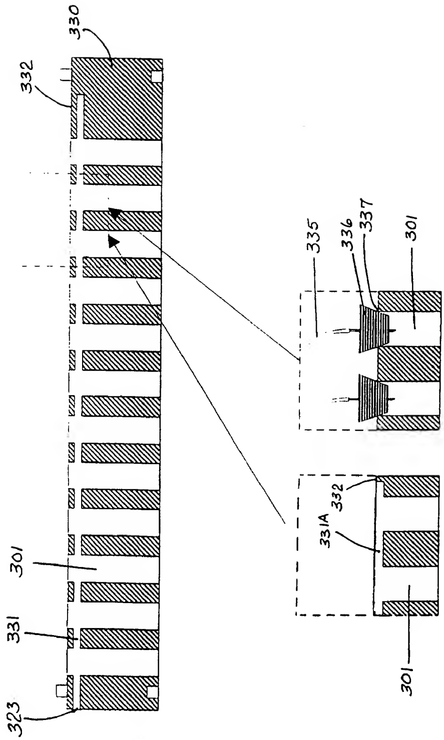


FIG. 11B

FIG. 11C

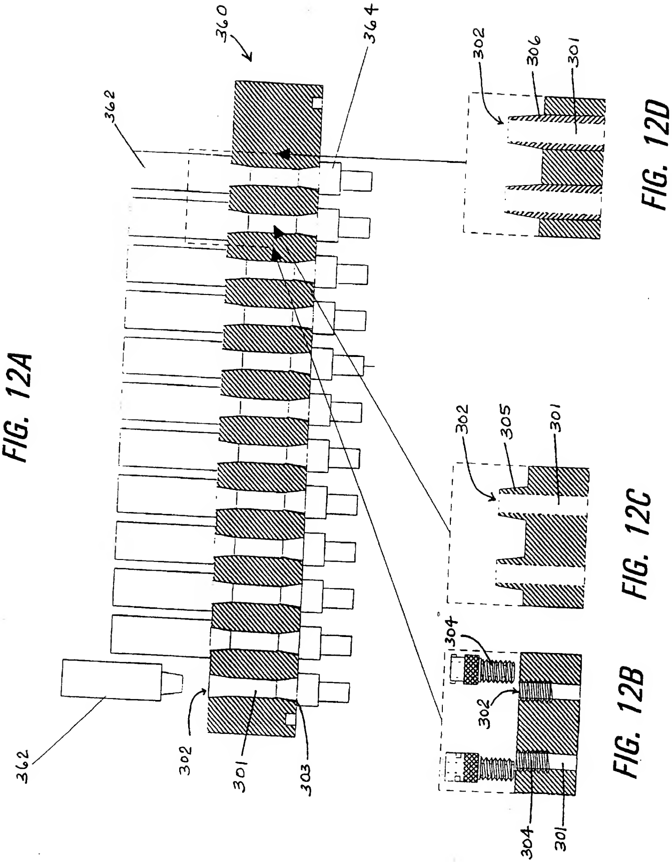


FIG. 12A

FIG. 12B

FIG. 12C

FIG. 12D

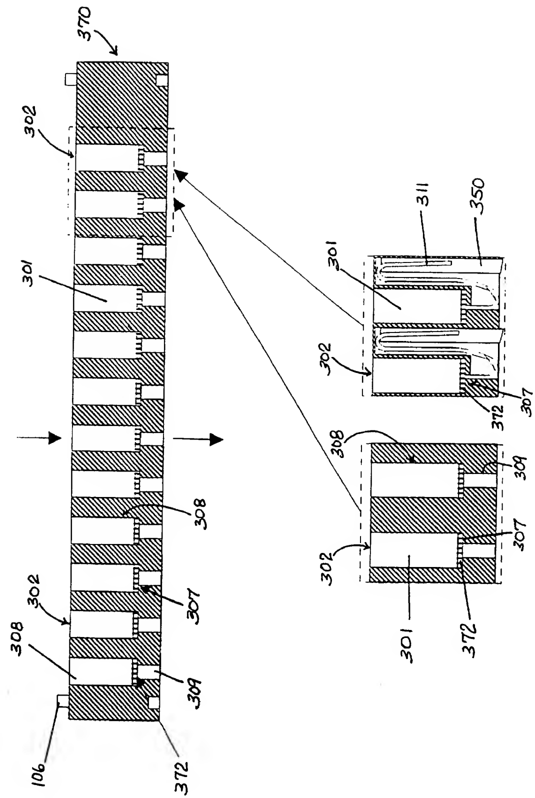


FIG. 13A

FIG. 13B

FIG. 13C